REMARKS/ARGUMENTS

The reply filed on August 22, 2007 was not considered fully responsive to the prior Office Action because the Examiner believes that Claim 15 as amended and amended claims 16-23 are no longer drawn to the elected subject matter for which applicant received a first action on the merits, mailed on February 22, 2007. The Examiner believes that newly amended claim 15 is directed to an invention that is independent or distinct from the invention originally claimed and elected with traverse. In particular, the Examiner has characterized the elected invention examined in the first office action, and specifically original claims 15-22, as being drawn to a method for inducing the activation and proliferation of natural killer (NK) cells comprising contacting the NK cells with a dendritic cell that can induce the activation and proliferation of NK cells, whereas amended claim 15, and dependent claims 16-23, are now drawn to a method for inducing the activation and proliferation of natural killer (NK) cells comprising contacting a human cell population comprising NK cells and monocytic dendritic precursor cells with an effective amount of GM-CSF and IL-15 to form immature dendritic cells and further contacting the population with a dendritic cell maturation agent to produce a mature dendritic cell which can induce the activation and proliferation of the NK cells in the cell population. The Examiner does not believe that thee claims as amended are drawn to contacting NK cells with a dendritic cell capable of inducing activation and proliferation, *i.e.*, a mature dendritic cell. As such, the Examiner has withdrawn claims 15-23 from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03 and since claims 15-23 are withdrawn, there are no claims pending that are drawn to the elected invention.

Applicants do not believe that the claimed invention is drawn to a non-elected invention, but in order to further expedite prosecution of the application, claim 15 has been further amended to recite "contacting a human cell population comprising NK cells with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and

interleukin 15 (IL-15)". The current amendment is believed to keep the subject matter of the invention being prosecuted to contacting NK cells with a dendritic cell capable of inducing activation and proliferation, *i.e.*, a mature dendritic cell. In this case mature dendritic cells that have been produced by previously contacting dendritic cell precursors with GM-CSF and IL-15. Such mature dendritic cell express increased levels of CD80 and CD86 as compared with mature dendritic cells isolated directly from an individual or mature dendritic cells produced from dendritic cell precursors that have been contacted with GM-CSF and IL-4.

Rejections Under 35 U.S.C. §112:

Claims 1-2, 4-5, and 15-16 stand rejected under 35 U.S.C. §112, first paragraph, because the Examiner believes that while the specification is enabling for mature dendritic cells derived from monocytic dendritic precursor cells cultured in GM-CSF and IL-15 that exhibit increased expression of CD80 and CD86 as compare to mature dendritic cells cultured in the presence of GM-CSF and IL-4 and are capable of increasing the proliferation of NK cells in culture by at least 10 fold or at least 30 fold after at least 7 days of co-culture, does not reasonably provide enablement for any dendritic cell with the claimed phenotypes of increased expression of CD80 and CD86 as compared to mature dendritic cells cultured in the presence of GM-CSF and IL-4 and the capacity to increasing the proliferation of NK cells in culture by at least 10 fold or at least 30 fold after at least 7 days of co-culture. Further, the Examiner does not believe that the specification enables any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Furthermore, the Examiner alleges that the specification fails to provide any guidance as to alternative culture conditions for producing immature or mature dendritic cells that share the same phenotype as the mature dendritic cells produced by culture of low-adherence dendritic precursor cells in GM-CSF and IL-15. The Examiner also alleges that the specification fails to provide any guidance as to whether dendritic cells with the claimed phenotype can be isolated from any mammal, or under what conditions or isolation techniques.

Applicant does not agree with the Examiner's characterization of the specification or the analysis of the prior art, but in order to further expedite prosecution of certain subject matter disclosed and claims in the specification Applicant has cancelled claims 1 through 6 without prejudice and amended claims 15 and 16. Therefore, the rejection as to claims 1 through 6 is moot. Claims 15 has been amended to recite "[a] method for inducing the activation and proliferation of natural killer (NK) cells, comprising: contacting a human cell population comprising NK cells with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15)" Further, claim 16 has been amended to recited "the mature dendritic cells" of claim 15. Applicant believes that the method of amended claims 15 and 16 is fully supported by the specification as filed. In particular, the Examiner is directed, for example, beginning at page 15, line 9 wherein methods for the culture of a human cell population comprising NK cells with dendritic cells that have been contacted with an effective amount of GM-CSF and IL-15 to induce the differentiation of immature dendritic cells and subsequently the culture of this cell population comprising the immature dendritic cells in an effective amount of a dendritic cell maturation agent. Subsequent to the recited method the number of NK cells in the cell population have increased substantially above the number that would have been obtained is the cell population were cultured with mature dendritic cells cultured in the presence of the standard cytokine mixture of GM-CSF and IL-4.

Applicant respectfully requests that the Examiner reconsider claims 15 and 16 and withdraw the rejection under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

Claims 4-5 and 22 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 have been cancelled without prejudice.

As to Claims 15-22, the Examiner believes that the claims are unclear and indefinite in that they encompass contact between the NK cells and dendritic cells *in vivo*, see dependent claim 19 in particular. For *in vivo* contact, the Examiner alleges that the claims are confusing in that no active steps for administering either a population of dendritic cells and/or a population of NK cells to a mammal are recited in the claims. Thus, the Examiner concludes that it is unclear whether the hand of man is actually part of the *in vivo* method and that the metes and bounds of the claims cannot be determined.

The Examiner further notes that Claim 22 recites the method of claim 21 "wherein the population of leukocytes are further contacted with antigen presenting dendritic cells." The Examiner alleges that it is unclear whether these dendritic cells are different from the dendritic cell with which the NK cell is contacted in the base claim, claim 15.

Without acquiescing to any remark of the Examiner, Applicant has amended claims 19 and 22, and added new claim 23. In particular, claim 19 has been amended to delete *in vivo* contact of the NK cells with mature dendritic cells. Further, claim 15 has been amended as set forth above. Amended claim 22 recites that the population of leukocytes of claim 21 can be further contacted with a population of antigen presenting dendritic cells and new claim 23 recites that the NK cells in the method according to claim 15 "are further contacted with an effective amount of a desired antigen." Applicant believes that each of these claims is fully supported by the specification as filed.

In particular, support for amended claim 15 can be found as set forth above in the rejection under 35 U.S.C. § 112, first paragraph. Support for amended claim 19 can be found in original claim 19. Pages 13 and 14, and Example 7, for example, provide support for amended claims 21 and 22 and new claim 23.

Applicant respectfully requests the Examiner consider and withdraw the rejection of claim 22 under 35 U.S.C. § 112, second paragraph in light of the amendments and remarks above.

Rejections Under 35 U.S.C. §102:

Claims 1-6 stand rejected under 35 U.S.C. §102(b) as being anticipated by Mohamadzadeh *et al.* (*J. Exp. Med.* 194:1013-1019, 2001). The Examiner alleges that Mohamadzadeh *et al.* teaches the preparation of immature dendritic cells by culturing monocytes in the presence of either GM-CSF and IL-15 or GM-CSF and IL-4. Further, the Examiner alleges that Mohamadzadeh et al. teaches maturation of the dendritic cells by treatment with LPS and that the mature dendritic cells produced from the culture of moncytic precursors in GM-CSF and IL-15 exhibited expression of CD1a, and high levels of CD80 and CD86. It has been noted by the Examiner that Mohamadzadeh *et al.* did not do a direct comparison of the phenotype of the IL-15 dendritic cells with the IL-4 dendritic cells, but that the IL-15 dendritic cells of Mohamadzadeh *et al.* were produced using the same culture conditions, *i.e.*, culture in IL-15 and GM-CSF, and appear to express the same markers. The Examiner has also noted that while Mohamadzadeh *et al.* did not test the ability of these cells to induce the proliferation or activation of NK cells, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent."

Applicant does not acquiesce to any comment of the Examiner regarding the teaching of Mahamadzadeh *et al.*, but to further expedite prosecution of certain subject matter disclosed and claimed in the present application claims 1 through 6 have been cancelled without prejudice. As such, this rejection is moot.

Claims 1-6 and 15-22 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/85920 A2, (Banchereau *et al.*). The Examiner alleges that Banchereau *et al.* teach the preparation of immature dendritic cells by culturing dendritic cell precursors in the presence of GM-CSF and IL-15, and the maturation of the dendritic cells by treatment with LPS or CD40L. The Examiner further alleges that Banchereau *et al.* teaches that the mature dendritic cells produced from the culture of dendritic precursors in GM-CSF and IL-15 exhibited expression of CD1a, and high levels of CD80 and CD86 and that the administration of the mature IL-15 dendritic cells to a patient to induce an immune response, where the IL-15

dendritic cells have further been exposed to antigen. The Examiner has noted that while Banchereau *et al.* did not do a direct comparison of the phenotype of the IL-15 dendritic cells with dendritic cells produced from culture in GM-CSF and IL-4, the IL-15 dendritic cells of Banchereau *et al.* were produced using the same culture conditions, i.e. culture in IL-15 and GM-CSF, and appear to express the same markers. Further, the Examiner has also noted that while Banchereau *et al.* did not test the ability of these cells to induce the proliferation or activation of NK cells, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent."

Applicant does not agree with the rejection or reasoning as set forth by the Examiner regarding the teachings of Banchereau *et al.*, but in order to further expedite prosecution of certain methods disclosed and claimed in the application have cancelled claims 1 through 6 without prejudice. Therefore, the rejection of claims 1 through 6 under 35 U.S.C. § 102(b) as anticipated by Banchereau *et al.* is moot.

As to the methods claims 15-22, the Examiner has noted that the methods as claimed contain a single method step, "contacting the NK cells with a dendritic cell." The Examiner alleges that dependent claim 19 clarifies that the "contact" can be "*in vivo*." Banchereau *et al.* is alleged by the Examiner to teach the *in vivo* administration of mature IL -15 dendritic cells to a mammal to induce an immune response and as such, as Mammals comprise NK cells, such *in vivo* administration of dendritic cells constitutes contact of dendritic cells with NK cells. The Examiner does note that Banchereau *et al.* teach the stimulation of T cells, not NK cells, but that it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable.

Applicant does not agree with the rejection of the Examiner as to the teaching of Banchereau *et al.*, but in order to further expedite prosecution of certain methods disclosed in the present application have amended claim 15 to recite "[a] method for inducing the activation and proliferation of natural killer (NK) cells, comprising: contacting a human cell population comprising NK cells with a dendritic cell that can induce the activation and proliferation of NK

cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15)." Further, claim 19 has been amended to delete the recitation of *in vivo*. The method of the invention now comprises the contact of the NK cells with mature dendritic cells that have been produced from dendritic cell precursors by contact with GM-CSF and IL-15 followed by contact with the dendritic cell maturation agent. All of the steps take place outside of the body. Banchereau *et al.* do not disclose or suggest such a method. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 1, 6, 15, and 18-21 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,849,452 (2/1/05), (Zitvogel *et al.*). The Examiner alleges that Zitvogel *et al.* teach methods for inducing the activation of NK cells comprising contacting resting NK cells with mature dendritic cells *in vitro* or *ex vivo*. Zitvogel *et al.* is further alleged by the Examiner to teach that the NK cells and dendritic cells can be contacted *in vivo* by administering the dendritic cells to a mammal and that contact between the NK cell and dendritic cell can lead to the proliferation of the NK cell . In addition, the Examiner alleges that Zitvogel *et al.* teach that the dendritic cells express IL-12, TNF-alpha, IL-15, and IFN α/β and that the NK cells can be population of leukocytes prepared by leukopheresis, or a highly enriched population of resting NK cells comprising more than 70% resting NK cells. The Examiner concludes that by teaching all the limitations of the claims as written, Zitvogel *et al.* anticipates the instant claims.

Applicant does not believe that Zitvogel *et al.* anticipates the present invention as claimed. In particular, amended claim 15 is directed to contacting a cell population comprising NK cells with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15). These culture conditions provide a mature dendritic cell that can induce the NK cells that exist in the cell population and any subsequent NK cells that can be added to proliferate and to become activated. Further, claims 18 through 20

have been amended. Claim 18 has been amended to recite that the dendritic cell that can induce the proliferation and activation of the NK cells is a mature dendritic cell. As above, claim 19 has been amended to delete *in vivo*. In addition, claim 20 has been amended the clarify that the cell population of claim 15 is further contacted with additional NK cells that are substantially isolated or that are provided as a population of leukocytes. The cell population can also be contacted with a population of mature dendritic cells that have been contacted with a predetermined antigen or with the predetermined antigen itself. In the first method, a population of dendritic cells can be produced by any number of methods that have been contacted and present the predetermined antigen. In the second method, the predetermined antigen is contacted, with for example, the immature dendritic cells and a dendritic cell maturation is added to mature the dendritic cell while it uptakes and processes the antigen for presentation. As such, Zitvogel does not anticipate or suggest the invention as presently claimed.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claim 15 and 18 through 21 under 35 U.S.C. § 102(e) as anticipated by Zitvogel *et al.* in light of the above amendments and remarks.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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